REMARKS

The Office Action of July 6, 2004 presents the examination of claims 34-50. The Examiner has deemed claims 47-49 to be directed to a non-elected invention. New claims 51 and 52 are added. Claims 34-52 are pending.

Claims 47-49 are improperly withdrawn from consideration

The Examiner has withdrawn claims 47-49 from consideration, asserting that they fall within the original, non-elected Group II. Applicant submits that this is incorrect.

The withdrawn claims 47-49 are directed to cells that comprise the expression cassette described by the examined claims 34-45. The original Group II recites claims directed to methods for transforming cells and cells made by those methods.

The withdrawal from consideration of claims 47-49 is incorrect. First, claims 47-49 are dependent from claims within the elected group and so do not represent an independent invention. Second, claims 47-49 are not described as products of any method of transformation. Third, the present application is a National Stage application of a PCT application and so the rules governing Unity of Invention govern restriction practice. In this regard, Applicant submits that the embodiments described in claims 47-49 share the common technical feature with the embodiments of claims 34-46 and 50 that the expression cassette

as recited in the examined claims 34-45 is an element of the claimed cells. Finally, it is the typical practice to examine nucleic acids, vectors and host cells harboring such nucleic acids as a single group of claims.

For all of the above reasons, Applicant submits that claims 47-49 should be rejoined to the present application.

Claim 34 is generic

The Examiner indicates that the present claim 34 is broadly generic, encompassing transmembrane domains of a receptor expressed in B or T cells, a genus of enhancers that are operative in a mammalian ES cell, primordial cell or bone marrow stromal cell, and an immunosuppressive protein. The Examiner takes a position that the incorporation of different nucleic acids encoding different proteins into the expression cassette described in claim 34 could change its utility. The Examiner agrees to examine claim 34 to the degree that its embodiments fall within the scope of the originally elected claims 1-17 and 30.

The Examiner is reminded of the broad, generic scope of original claim 1. The original claim 1 recited:

> [An] expression cassette, characterized in that under the genetic control of an organ-specific or tissue-specific promot[e]r and optionally one or more other regulatory elements 3' downstream of the promot[e]r,

> it encompasses the coding nucleotide sequence of at least one non-immunogenic receptor which is located on the cell surface.

The original claim 1 is thus seen as of even broader generic scope than the present claim 34. For instance, the present claim 34 recites the "organ-specific or tissue-specific promoter" as one that comprises a cardiac muscle-specific promoter linked to an enhancer effective in a mammalian ES cell, primordial cell or bone marrow stromal cell. Claim 34 recites the "non-immunogenic receptor" as a transmembrane domain of a receptor expressed in B or T cells. Thus, the scope of claim 34 is entirely within the scope of original claim 1 and claim 34 should be examined in its entirety. The Examiner is welcome to perform an initial examination of any particular species within claim 34. However, should that species be found to be allowable subject matter, the Examiner should proceed to examine additional species of claim 34 with an eye toward determining patentability of the full scope of the generic claim.

Rejection under 35 USC § 112, first paragraph

Claims 34-36 and 50 stand rejected under 35 USC § 112, first paragraph, as allegedly claiming subject matter beyond the original description, *i.e.* introducing new matter into the

application. Reconsideration and withdrawal thereof are requested.

The Examiner takes a position that, as to the promoter to be used at the step of selecting transformed cells, the generic nature of the invention was not adequately described in the original application. Similarly, the Examiner asserts that the specification fails to provide any generic description of a "constitutive" enhancer.

Applicant disagrees. Applicant has specifically indicated in their previous Amendment where support for each limitation in the new claims is provided by the specification. This specifically included mention of support for a constitutive enhancer as a genus. Applicant again notes the generic concept of an enhancer is mentioned at, *e.g.*, page 10, line 5 of the specification and the CMV enhancer is mentioned as a specific example of such at, *e.g.*, page 13, line 3. Applicant furthermore asserts that the artisan of ordinary skill would recognize that the CMV enhancer is a strong, constitutive enhancer. This is evidenced by the attached Exhibit 1, a page from a catalog of a molecular biology supply company, which describes a vector including a CMV promoter/enhancer as one that "allows strong constitutive expression in many cell types."

The specification also well-describes the aspect of the invention that the promoter operative in mammalian ES cells,

primordial cells or bone stromal cells is used to drive expression of the selectable marker gene used for selecting initially transformed cells. Thus, Applicant also considers that the skilled artisan would recognize the generic nature of the promoter used at the step from the example of the PGK promoter and the text at, *e.g.* the last paragraph on page 10 to the first paragraph on page 11 (which describes the initial selection step) and the text at page 20, lines 19-21 (describing use of the PGK promoter for use in driving the gene for initial selection of transformed ES, primoridial or bone marrow stromal cells). The Examiner should also consider Figure 1, which shows that the first step in the transformation process is one in which selection of transformed human or murine embryonal stem cells (*i.e.* ES cells) is performed by selection using an antibiotic, resistance to which is expressed by a gene under the control of a PGK promoter. ("CMV-neo" is the name of the vector as a whole.) Finally, the Lallemand reference cited by the Examiner as prior art describes the PGK promoter as one that is active in the primordial germ cell.

For all of the above reasons, the Applicant submits that the specification is <u>not</u> "silent with respect to the genus of promoters that is operative in a mammalian ES cell.", etc. Indeed, the specification well-describes the generic concepts of the various promoter elements used in the claimed expression

cassettes and provides a working example of each. Thus, the rejection of claims 34-46 and 50 under 35 USC § 112, first paragraph, as introducing new matter into the application should be withdrawn.

Still further, the Examiner should note that claims 35 and 36 individually limit the enhancer and promoter, respectively. Claim 37 limits both the promoter and enhancer recited to a PGK promoter and CMV enhancer, respectively, and therefore at least claim 37 should be free of this ground of rejection.

The Examiner further rejects claim 34, in parts (C), (D) and (E through I) under 35 USC § 112, first paragraph, for alleged failure of the specification to provide enabling disclosure of the claimed invention. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Examiner indicates that these parts of claim 34 recite that a promoter constitutively operative in mammalian ES cells is operatively linked to a cardiac muscle-specific promoter. Therefore such promoter would not function in ES cells because it is linked to a cardiac muscle-specific promoter, nor would the promoter function in cardiomyocytes because it is linked to an ES cell-specific promoter.

The Examiner apparently fails to understand the structure of the claimed constructs. The embodiment (C) in claim 34 includes two separate promoters, one that is functional in ES cells and one that exhibits tissue specificity by preferentially driving transcription in cardiomyocytes. The Examiner may be confusing a constitutive enhancer with a constitutive promoter. The linkage of an ES specific enhancer to a cardiac-specific promoter merely upregulates somewhat the function of the cardiac muscle-specific promoter when it is present in an ES cell. It does not abolish the large increase in activity of the cardiac muscle-specific promoter in cardiomyocyte cells compared to other cell types.

As evidence of this sort of expression profile, Applicant submits Exhibit 2, which is a paper describing the expression profile of a promoter constituted by a CMV enhancer attached to a tissue specific promoter. Exhibit 2, Liu et al., *Gene Therapy*, 11:52-60 (2004), at Figure 1c, shows that a low, basal level of expression of a reporter gene driven by a CMV-PDGF enhancer-promoter is achieved in *e.g.* kidney cells (COS-7), while approximately 6-fold higher expression is seen in neuronal cells (PC12, C17.2) representing the tissue in which the PDGF promoter is deemed specific. The authors conclude that the hybrid promoter has retained the "neuronal characteristics of the PDGF promoter."

In view of the above, Applicant submits that the Examiner has failed to establish a *prima facie* lack of enablement of claim 34, in parts (C), (D) and (E through I) and the instant rejection should be withdrawn.

Rejection under 35 USC § 112, second paragraph

Claims 34-46 and 50 are rejected under 35 USC § 112, second paragraph, as being indefinite. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The first basis for this rejection indicated by the Examiner is that claim 34 recites, "an expression cassette comprising polynucleotides" selected from A-E. The Examiner states that such recitation makes it indefinite whether one or more of the polynucleotides A-E is to be included in the cassette.

Claim 34 is amended to clarify that one or more of the polynucleotides A-E can be included in the cassette. The Examiner should note that Figure 1 illustrates an embodiment of the invention in which the expression cassette includes a polynucleotide (A) and a polynucleotide (B).

Claim 34 is further rejected because the Examiner considers the location of the IRES element within the cassette to be unclear. Applicant submits that the relationship between the

IRES and the promoter not unclear. The Examiner should note the drawing Figure 1, and the description in the specification that the expression cassette is typically bicistronic. See, *e.g.* page 11, line 18. The Examiner should further note the arrangements described at page 12, last paragraph to page 13, line 2 of the specification.

The Examiner further asserts claim 34 is indefinite in the recitation of a promoter constitutively operative in mammalian ES cells linked to a cardiac muscle-specific promoter. Applicant has explained the fault of the Examiner in reaching this interpretation of the claims above.

The Examiner further asserts that claim 34 is indefinite in the phrase in part (C), "operatively linked to a polynucleotide." Applicant disagrees, but have nonetheless amended claim 34 to describe operative linkage of an enhancer to to a promoter as a "promoter-enhancer". Applicant submits that this amendment clarifies which linkages are between promoters and enhancers and which linkages are between promoters or "promoter-enhancers" and polynucleotides, thus obviating this ground for rejection.

The phrase "protein provides a selectable or screenable marker gene" is deemed unclear. The word "gene" has been deleted to clarify the language of the claims.

The Examiner finds no antecedent basis for the phrase, "the at least one angiogenesis factor" in claim 45. Claim 45 is ultimately dependent upon claim 34, which recites such angiogenesis factor in parts (A) through (E).

Claim objections

The Examiner has objected to the format of the claims for various minor informalities. The claims are amended to correct these deficiencies (the lack of the phrase "polynucleotide encoding a ..." was only found in part (C) of claim 34) and to spell out the abbreviations "ES", "IRES" and "PGK" at their first use in the claims.

As to the function of the "secreted protein", the Examiner has overlooked the term "immnosuppressive"; the complete phrase as used in claim 34 is "secreted immunosuppressive protein." Such states a function for the protein.

Rejection under 35 U.S.C. § 103(a)

Claims 34-46 and 50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over of Klug, Gaines, Griscelli, Wolfgang-M and Mack (claims 34 (A) and (B) and dependent claims), together with Graham and Lallemand (claims 34 (C)-(E) and dependent claims). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicant again submits that the Examiner fails to establish *prima facie* obviousness of the claimed invention. Applicant has previously explained that the cited references do not describe or suggest each and every limitation of the present claims. For example, at least the recitation of "at least one IRES operatively linked to at least one polynucleotide encoding an angiogenesis factor" is not described or suggested by any reference, and is therefore absent from their combination.

The Examiner is further reminded that there must be motivation provided, either by the references themselves or by the state of the prior art as established by evidence, to make modifications of the prior art to obtain the claimed invention. Such motivation is a requirement of a proper case of *prima* facie obviousness, to prevent the Examiner from improperly using the claims as a template upon which to assemble prior art. Such an approach to an obviuousness rejection constitutes improper hindsight reconstruction of the invention (*see, e.g. In re Rouffet,* 47 USPQ2d 1453 (Fed. Cir. 1998) and such is exactly what has happened in the present instance.

Applicant submits that the required motivation is entirely lacking in the present instance. For example, the Examiner fails to describe the motivation to combine an IRES with a polynucleotide encoding an angiogenesis factor from among all

the possible coding sequences with which an IRES might be combined.

As the combined references fail to describe each element of the instant invention, and further fail to describe or suggest any motivation to select those elements and arrange them in the manner described by the claims, the Examiner fails to establish *prima facie* obviousness of the invention. Accordingly, the instant rejection should be withdrawn.

Furthermore, Applicant has previously explained that the invention as claimed provides some result, that is production of a pure or very nearly pure culture of cells that express the physiologic properties of cardiomyocytes, that is unexpected in view of the cited references. The Examiner dismisses Applicant's argument about unexpected results on the grounds that the claims are not limited by the physiological properties of the cells obtained by the method.

Applicant disagrees that the result obtained by the method of claim 50 using the expression cassettes of the claims 34-46 can be ignored in this fashion. It is not necessary for the claims to recite the advantage obtained by the invention; it is only necessary that the unexpected result be achieved due to such structure as is recited in the claims. *In re McLaughlin*, 170 USPQ 209 (CCPA 1971). In the present instance, Applicant has explained that the expression cassette

as claimed in claims 34-46 and 50 is what enables the desired level of purification and identification of the very small population of cells that exhibit the desired physiologic properties. Recitation of those properties in the claims to the expression cassette is thus not required.

Furthermore, the Examiner should consider that the present application includes claims to cells that do recite the described physiological properties. However, the Examiner has improperly withdrawn them from consideration. At least claims 47-49 should be found unobvious (and rejoined to the instant application) over the cited references. Finally, claim 50 is amended to recite that the method used results in obtaining cells having the properties upon which the unexpected result relies. Accordingly, at least claims 50-52 should be found unobvious over the cited references.

The present application well-describes and claims patentable subject matter. The favorable action of allowance of the pending claims and passage of the application to issue is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at the telephone number of the undersigned below, to

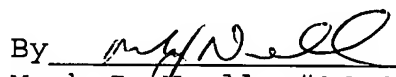
conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), Applicant respectfully petitions for one (1) month extension of time for filing a response in connection with the present application. The required fee of $55.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By 
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Attachments: Exhibits 1 and 2